REMARKS UNDER 37 CFR § 1.111

Formal Matters

Claims 69-88 are pending after entry of the amendments set forth herein.

Claims 34-38 and 40-60 are canceled without prejudice.

Claim 69 is amended.

Support for the amendments is found throughout the specification, and at, for example, page 5, line 25 to page 6, line 11, and original claim 33, as well as in earlier-presented claims.

Applicants respectfully request reconsideration of the application in view of the amendments and remarks made herein.

No new matter has been added.

Interview Summary

Applicants wish to express their gratitude to Examiner Souaya for the telephonic interview on January 29, 2003 with Dr. Irena Merenkova and the undersigned. The outstanding rejection of the claims were discussed, as well as amendments and arguments to overcome such rejections. These amendments and arguments are presented herein, which in applicants view place the present claims in form for allowance.

Rejection Under §103(a)

In the Final Office Action mailed September 4, 2002, all pending claims were rejected as being unpatentable over Kuppuswamy et al. in view of Hoogendoorn et al. This rejection is respectfully traversed as applied, and as it may be applied to the present claims.

The present claims are directed to detection of a polymorphic nucleotide using a primer extension reaction using an extension reaction mixture that includes:

1) a primer that specifically hybridizes to the target sequence such that the 3' end of the primer is at least one nucleotide 5' of a variant nucleotide of the polymorphic site, and

2) a plurality of deoxyribonucleoside triphosphates (dNTP) or ribonucleoside triphosphates (rNTP), where the plurality of dNTPs or rNTPs provide for at least one

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nucleotide extension of the primer when hybridized to a target sequence having either of the two variant nucleotides,

and excludes:

3) a dNTP or rNTP complementary to one of said variant nucleotides of the polymorphic site,

4) dNTPs or rNTPs that are detectably labeled or modified, and

5) dideoxynucleoside triphosphates (ddNTPs).

After performing the primer extension reaction, the reaction products are analyzed.

As discussed during the interview, one advantage of the claimed invention is that a single reaction mixture provides for detection of both the presence and absence of the variant of interest in the polymorphic site of the target sequence. In addition, a single reaction allows one to determine whether the organism from which the target sequences are derived is heterozygous or homozygous. These advantages are accomplished through careful design of the primer so that at least some primer extension occurs both when the variant nucleotide is present and when the variant nucleotide is absent.

Kuppuswamy and Hoogendoorn, either taken alone or in combination, do not provide the claimed invention.

First, if the ordinarily skilled artisan were to combine Kuppuswamy and Hoogendoorn to substitute the detectable label detection method of Kuppuswamy with the detection of extension products by length of Hoogendoorn as suggested by the Office Action, s/he would use ddNTPs in the extension reaction mixture as per Hoogendoorn's teaching. S/he would not "have immediately seen from Kuppuswamy et al. that the dideoxynucleotides of Hoogendoorn et al. would not be necessary because Kuppuswamy et al. taught a method which used no dideoxynucleotides" because:

1) Kuppuswamy is either silent as to ddNTPs or did not require ddNTPs since such are not important to detection using detectably-labeled dNTPs

2) Kuppuswamy also teaches that separate reactions should be performed for each variant nucleotide; and

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2) the length-based detection method of Hoogendoorn simply would not be operable without such ddNTPs.

The claimed invention -- which explicitly does not use either detectably-labeled nucleotides and explicitly does not use ddNTPs is thus not obvious from the combination of Kuppuswamy and Hoogendoorn. The claimed invention uses primer design and selection of the dNTPs (or rNTPs) in the reaction mixture so as to require that primer extension occur regardless of the variant nucleotide present in the target sequence, the invention avoids the need for either detectable labels or ddNTPs.

Second, neither Kuppuswamy nor Hoogendoorn, either taken alone or in combination, suggest that detection of the presence/absence of a variant nucleotide of a polymorphic site can be detected in a single reaction **without using 1) either a detectably labeled dNTP to detect primer extension (Kuppuswamy) OR 2) ddNTPs to terminate the reaction should a particular variant nucleotide be present in the target sequence (Hoogendoorn).**

As noted above, the claimed invention uses primer design and selection of the dNTPs (or rNTPs) in the reaction mixture so as to require that primer extension occur regardless of the variant nucleotide present in the target sequence.

If one combined Kuppuswamy and Hoogendoorn as suggested in the Office Action so that the detectably labeled dNTP of Kuppuswamy was substituted with the length-based detection method of Hoogendoorn, a single reaction would not provide for detection of both the presence and absence of the variant nucleotides of interest in the target sequence.

For example, Kuppuswamy shows that the primer is positioned immediately adjacent the variant nucleotide (see Kuppuswamy Fig. 1). Extension only occurs when one of the variant nucleotides is present. In a method based on the combined reference, so that Kuppuswamy is performed without a detectably labeled dNTP (and without ddNTPs) and the reaction products are analyzed based on length, the presence of unextended primer in the reaction product could not be relied upon to indicate that one of the possible variant nucleotides was not present in the target sequences. This same result would occur if there was excess primer in the reaction mixture. This is at least one reason why there is no teaching or suggestion in either of Kuppuswamy or Hoogendoorn that SNP analysis can be accomplished using one extension reaction, and without the need to use ddNTPs.

In addition, this also means that a method based on the Office Action's suggested

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combination of Kuppuswamy and Hoogendoorn, each of which only teach a primer that is immediately adjacent the variant nucleotide (i.e., the next nucleotide after the 5' end of the hybridized primer is the variant nucleotide) could not be used to determine whether an individual from whom the sample was obtained was heterozygous or homozygous. Unextended primer in a reaction mixture after completion of the extension reaction could be due to the presence of either the other variant nucleotide (detected by unextended primer) or excess primer that simply did not hybridize or that was not extended. Thus, the only result that the cited art can confirm, where the art is modified as suggested by the Office Action, is that one of the variant nucleotides is present. The presence of unextended primer can not be relied upon to indicate that the other variant nucleotide is present in the target sequence. Thus, the art teaches that one must conduct two different extensions reactions in order to detect the presence/absence of the two variant nucleotides.

In view of the above, applicants respectfully submit that the claimed invention is not obvious in view of the cited art, and the rejection can be withdrawn.

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Conclusion

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number TGEN-001.

Respectfully submitted,
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Date: Feb 13, 2003

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